

REMARKSThe Invention

At the outset, Applicants and the undersigned wish to thank Examiners Prasthofer and Venkat for the extremely helpful personal interview held on October 17, 2001. As discussed during the interview, the invention features methods for performing high throughput screens of combinations of compounds to discover combinations that interact in biological systems. The methods of the invention can identify effective therapeutic combinations of compounds that exhibit previously unknown therapeutic effects even where each compound in the combination may have previously have no recognized biological effect, and even where the compounds in the combination would not, *a priori*, have been obvious candidates to use in combination.

The Office Action

Claims 1-63 are pending. Claims 13, 19, 25-27, 36, 45-47, and 52 are withdrawn from consideration. Claims 1-12, 14-18, 20-24, 28-35, 37-44, 48-51, and 53-63 stand rejected for lack of enablement and for obviousness over U.S. Patent No. 5,650,489 to Lam et al. (hereafter "Lam") in view of U.S. Patent No. 5,756,304 to Javonovich et al. (hereafter "Javonovich") and further in view of U.S. Patent No. 5,985,356 to Schultz et al. (hereafter "Schultz"). Claims 1, 11, 17, 18, 34, 35, 51, and 60-62 further stand rejected for anticipation by Lam. Claims 1, 11,

17, 18, 28, 29, 35, 48, 51, and 60-62 further stand rejected for anticipation by Gallop et al. (J. Med. Chem. 37:1233-1241, 1994; hereafter "Gallop").

Applicants note that the Examiner who issued the Office Action is no longer with the PTO; these Remarks, therefore, are directed to the Office rather than the Examiner.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-12, 14-18, 20-24, 28-35, 37-44, 48-51, and 53-63 were rejected for lack of enablement; *i.e.*, the claims are purportedly broader than the scope of enablement provided by the specification.

The scope of enablement rejection pertains to two claim terms: "test element" and "compounds."

Applicants note that the Office Action does not expressly reject the claims based on the "test element" phrase; the Action could be read to imply that the claims have been limited, in this respect, to lung cancer cells, by virtue of a § 121 election. Prior to the present amendment, none of the claims has been amended, to lung cancer cells or in any other respect. Thus, as the undersigned discussed with Examiner Prasthofer by telephone on August 3, 2001, the discussion in the Office Action of the scope of the claim term "test element" is addressed herein as an overbreadth/lack of enablement rejection under 35 U.S.C. § 112, ¶ 1, there having been no agreement by applicants that the claims should be amended to be limited to lung cancer cells.

As to this rejection, applicants first note that claim 1 has been amended to replace "test element" with the narrower term "living cell." Support for this amendment is found throughout the specification, *e.g.*, on page 8, where the use of numerous cell types is discussed. The same methods used to test combinations of compounds against lung cancer cells can be used to test compound combinations against any living cell type; in accordance with the enabling instructions provided in the specification, other cell types have been used by applicants, in essentially the same manner as the methods used for lung cancer cells, and successful results have been obtained, as with lung cancer cells. The Office is directed to co-pending U.S. Patent Application Serial No. 60/304,089, which describes experiments using the methods of the invention to discover combinations of compounds that produced synergistic results on another cell type, peripheral blood mononuclear cells (PBMCs).

Turning next to the second scope of enablement issue, relating to the claim term "compounds," the basis of the rejection appears to be the Office's assertion that the specification does not specify the compounds to be tested. This is incorrect. The specification is replete with teachings of compounds that can be tested using the claimed methods. For example, on page 2 of the specification, applicants describe combinatorial chemistry libraries, peptidomimetic libraries, and natural products libraries. At page 12 of the specification, applicants provide more details:

The compounds can be synthetic or naturally occurring (*e.g.*, prostaglandins, lectins, naturally occurring secondary metabolites,

hormones, etc.). Large libraries of such molecules, in purified form, are available in pharmaceutical companies, chemical companies, and academic laboratories; such libraries also can be synthesized using known combinatorial chemistry techniques.

Applicants have provided sufficient teaching regarding the sources and types of compounds to be tested. Applicants have also provided guidance regarding the selection of compounds; as is described throughout the specification, any compound can tested in the claimed methods, regardless of whether it is a small molecule (*e.g.*, an FDA-approved small molecule) (page 8, line 27, to page 9, line 1, of the specification) or a compound having no known biological activity (page 12, lines 18 and 19, of the specification).

The Office suggests that “referring to compounds by name *e.g.*, sodium chloride, magnesium sulfate, or Cephalosporin C would be more helpful in the practice of [the claimed invention]” This statement appears to indicate a misunderstanding of the invention. The methods of the invention are high-throughput screens of combinations of compounds. Any combination – of any of thousands of compounds -- can be tested according to the invention; naming a few of them in the manner suggested by the Examiner is completely beside the point, and would have no effect on the issue of enablement. Libraries of any size, from any source, can be used in the screening methods of the invention, without any prior knowledge of the structure or name or source of any compound tested in combination with other compounds. Possessing none of this knowledge, a practitioner can discover, using the methods of the invention, unique combinations of compounds that have previously unknown therapeutic efficacy. The claims are

directed to screening large numbers of combinations of compounds, regardless of the source, and the name, source, and structural formulae of the compounds are totally immaterial.

The Office states that "it would require the testing of an excessive amount of compounds to determine which "natural" compounds fit the description of combinations as claimed." But screening large libraries for efficacious combinations is the point, indeed the principal objective, of the invention. The Office has presented no evidence or reasoning to support the proposition that such high throughput screening is not enabled. Moreover, some of the screening methods used in the invention were standard techniques that were well-known to those skilled in the art at the time the invention was made, and these are thoroughly described in the specification.

Lam and Gallop, two references cited by the Office in support of a rejection of some of the claims over the prior art, support enablement. As is described in more detail below, each of these references describes screening large numbers of compounds to identify single compounds having a desired activity (Lam describes the testing of a library containing nearly 2.5 million compounds; Gallop describes the testing of a library containing 64 million compounds). Thus, while these two references do not anticipate or make obvious the claimed invention (see below), they provide compelling evidence of enablement.

Rejections Under 35 U.S.C. §§ 102(b) and 103(a)

Claims 1, 11, 17, 18, 34, 35, 51, and 60-62 were rejected for anticipation and/or obviousness in view of Lam. Claims 1, 11, 17, 18, 28, 29, 35, 48, 51, and 60-62 were rejected for anticipation by Gallop. Applicants respectfully traverse these rejections.

According to the Office, Lam “discloses a method of screening which involves a combination of compounds with the objective of determining which combination exerts a desired characteristic such as altered rate of cell proliferation. ... The disclosures of Gallop et al. read on the instantly claimed invention because it describes a method of screening which utilizes combinations of amino acid entities, the objective of which is to identify combinations with desirable bioactivity.”

Each of these statements is incorrect. Lam and Gallop describe methods for identifying single compounds having a desired biological activity, not methods for identifying active combinations of compounds.

In support of the assertion that Lam describes methods for identifying active combinations of compounds, the Office states that, in Lam’s method, more than one compound-containing bead may be added per well. What the Office fails to note is that, in the next step, Lam partitions the compounds in order to identify individual compounds (not combinations) that are active. For example, at column 22, lines 41-53, Lam states:

A library of sequentially cleavable bio-oligomers is prepared and distributed in wells of microtiter plates such that each well contains

more than 50, and more preferably from about 50 to about 250, beads per well. The beads are treated so as to cleave about 1/3 of the bio-oligomers. Supernatant is assayed for biological activity in a replicate plate. Beads from wells demonstrating biological activity are then suspended and distributed into wells of a microtiter plate so that each well contains about 1-10 beads. The beads are treated to release another 1/3 of bio-oligomer, and the supernatant assayed for biological activity. Beads from wells demonstrating biological activity are isolated and the attached bio-oligomer is sequenced. When more than one bead is found, all the identified sequences are prepared and individually tested for biological activity. This two step sequential biological assay provides an efficient, powerful method to screen a very large library for bio-oligomers with specific biological activity. (Emphasis added)

From this passage, it is clear and unambiguous that Lam is describing screening individual compounds; he is not testing combinations of compounds.

Turning now to Gallop, the Office states that “[a]ll possible combinations of amino acids with activity exceeding some threshold are then prepared and tested to identify explicit sequences with potent activities.” (Emphasis omitted). The Office has misinterpreted the meaning of the word “combination” in this passage: Gallop is referring to the testing of individual compounds (hexameric peptides), each of which consists of six amino acids joined by peptide bonds. In short, Gallop does no more than describe the testing of single compounds with different amino acid sequences. Gallop makes absolutely no mention of testing combinations of compounds. Moreover, as is clearly stated in the passage cited by the Office, Gallop’s stated goal of “identifying explicit sequences with potent activities” is limited to the identification of individual compounds (*i.e.*, peptides) having a desired effect.

Having now placed Lam and Gallop in proper context, applicants turn to the rejected claims.

The independent claims rejected for anticipation by Lam and Gallop are claims 1, 60, and 61. Claims 28 and 48 were rejected for anticipation by Gallop. For the reasons given below, none of these claims is anticipated by the cited references.

Claims 1, 28, 48, and 60

Claims 1, 28, 48, and 60 are directed to methods for screening two-compound or higher order combinations for biological activity by testing the ability of combinations of compounds to alter a property of living cells. Step (f) of claim 1, and step (e) of claims 28, 48, and 60, recite selecting combinations of compounds that cause an effect on this property of the test cells that is different from the effect of either compound of the combination by itself. In other words, merely identifying a combination of compounds that alters the test cell property compared to untreated control cells is not enough; it is still possible (and, in fact, is highly probable) that the test cell property is altered by only one component of the combination, with the other components having no effect. The claims require that the activity of the combination be compared with that of each of its components, and combinations exhibiting greater activity than the activity of each component alone be selected. This is in stark contrast to Lam and Gallop, which,

as is discussed above, simply describe methods of identifying individual compounds having a particular activity.

An illustration of why this comparison step is key to the practice of the invention is found in the Table on page 36 of the specification. When tested on A549 lung carcinoma cells, the combination of podophyllotoxin and paclitaxel was discovered to have an antiproliferative activity of 6.3, relative to a vehicle-only control. Only when compared with podophyllotoxin-only and paclitaxel-only controls does it become apparent that the antiproliferative activity resides primarily in the paclitaxel, and not with the combination. The identification of an individual antiproliferative compound such as paclitaxel is similar, for example, to the results one could expect using Lam's method.

The power of the claimed methods is revealed when the antiproliferative activity of the combination of bepridil and promethazine is compared to that of the individual components. Alone, bepridil and promethazine have antiproliferative activities of 1.8 and 1.3, respectively. When combined, in the method of the invention, these two compounds, totally unexpectedly, exhibit an antiproliferative activity of 15.2. This result illustrates the power of the invention to identify novel combinations of compounds that, alone, are unremarkable in their activities, but in combination are uniquely effective.

A potent combination such as bepridil and promethazine could not be identified using the methods of Lam or Gallop, in which components of mixtures having a desired activity are tested individually, not in combination. Indeed, Lam

and Gallop clearly fail to recognize that activity may be present in a combination, yet be absent or insignificant in the individual constituents of the combination.

For all of the foregoing reasons, applicants respectfully request that the rejection of claims 1, 28, 48, and 60 (and claims dependent therefrom) for anticipation by Lam and Gallop be withdrawn.

Claim 61

Claim 61 (as amended), like claims 1, 28, 48, and 60, includes the step of selecting combinations of compounds that cause an effect on test cells that is different from the effect of each compound of the combination by itself. As is described above, this step is neither taught nor suggested by either Lam or Gallop, and for this reason alone the rejection of claim 61 should be withdrawn. In addition, as is described below, claim 61 contains further limitations that are neither taught nor suggested by Lam or Gallop.

Claim 61 reads:

61. A method for screening combinations of compounds for biological activity, said method comprising the steps of:
- (a) providing living test cells,
 - (b) contacting said test cells with at least 100 compounds under conditions that ensure that each compound/test cell contacting is segregated from the others,
 - (c) detecting or measuring a property of said test cells,
 - (d) selecting compounds that cause a change in said property relative to said property of said test cells not contacted with said compounds,
 - (e) creating an array of at least 49 unique two-compound or higher order combinations from the identified compounds,

(f) contacting said array of combinations of compounds with test cells under conditions that ensure that each compound combination/test cell contacting is segregated from the others,

(g) detecting or measuring a property of the test cells of step (f), and

(h) selecting combinations of compounds that cause an effect on said property of step (g) that is different from the effect of each compound of the combination by itself.

Claim 61 recites the activity rank-order screen method exemplified on page 28 of the specification. In this screen, compounds are initially individually tested and ranked by activity. Compounds that cause a desired change in a property of the test cells are then selected and tested in combination. After again detecting a property of the test cells, combinations of compounds that cause an effect on the property of the test cells are selected.

Lam and Gallop each fails to teach or suggest first testing the individual compounds, and then combining compounds, based on the individual results. As is discussed above, the screening techniques of Lam and Gallop identify only individual compounds having a desired activity. The aim of Lam and Gallop, in which compounds are combined in one well (referred to as "pooling"), is to reduce the number of wells that must be assayed. The strategy employed by Lam and Gallop inherently relies on two assumptions: (1) that a small minority of compounds will have the desired activity; and (2) that a desired activity will rarely be (i) present in the presence of combinations of compounds and (ii) absent when the compounds of the combinations are tested individually. Having already tested the compounds individually, one following the method of Lam or Gallop would

have no reason to test compounds in combination. If anything, Lam and Gallop teach away from the method of claim 61.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-12, 14-18, 20-24, 28-35, 37-44, 48-51, and 53-63 were rejected for obviousness over Lam in view of Javonovich and in further view of Schultz. Applicants respectfully traverse this rejection.

The M.P.E.P. § 2143 states that to establish a *prima facie* case of obviousness, the prior art references must, in combination, teach or suggest all of the claim limitations. The three references cited by the Office do not do so, as to any of the rejected claims. *I.e.*, even if there were something in the references to motivate their combination, such combination would not contain all of the limitations of any of the rejected claims.

Lam, as is discussed above, describes screening for individual compounds having a desired activity. Lam does not teach or suggest selecting combinations exhibiting altered biological activity relative to that exhibited by each component alone, as is required by the claims. Lam fails even to recognize that a combination of compounds could possess a biological activity greater than that of the individual compounds alone.

The deficiencies of Lam are not remedied by either Javonovich or Schultz. As is noted by the Office, Javonovich teaches the use of robotic screening of compounds, and Schultz teaches the use inkjet printing in combinatorial

chemistry. Like Lam, however, Javonovich and Schultz both fail to teach or suggest selecting combinations exhibiting altered biological activity relative to that exhibited by each component alone. Thus the combination of all of the references fails to teach or suggest all of the limitations of any of the independent claims.

As is summarized in the Interview Summary Record, during the interview the inventors presented data showing the activities of several combinations of compounds discovered using the high throughput screening methods of the invention. These were instances in which two compounds, individually, had little biological effect, but together demonstrated very high activity. Such combinations could not have been discovered except by the methods of the invention. Furthermore, in a number of instances, the synergy between the two compounds was limited to the desired biological effect, and did not extend it to activities likely to cause undesirable side effects. One example was the combination of Amoxapine and low-dose Prednisolone. This combination had higher desired activity (*e.g.*, TNF- α suppression *in vitro*, IL-1 β suppression *in vivo*) than high dose Prednisolone, but desirably failed to damage joints in rodent paws examined histologically, compared to high-dose Prednisolone.

In view of the foregoing remarks, Applicants respectfully request that the rejection of claims 1-12, 14-18, 20-24, 28-35, 37-44, 48-51, and 53-63 for obviousness be withdrawn.

Conclusion

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested.

Examiner Prosthofor indicated during the interview that he might be telephoning the undersigned with a species election for search purposes, to determine whether there exists any relevant prior art. The undersigned has conferred with the inventors, and will make such an election should Examiner Prosthofor telephone with that request.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Version of claims with markings to show changes made

1. (Amended) A method of screening two-compound [two-entity] or higher order combinations for biological activity using at least seven compounds [entities] in at least a seven-by-seven combinational array comprising at least forty-nine unique combinations of compounds [entities], said method comprising the steps of:

- (a) providing said compounds [entities],
- (b) creating said array of combinations of compounds [entities],
- (c) providing [a] living test cells [element comprising one or more distinct biological moieties],
- (d) contacting said array of combinations of compounds [entities] with said test cells [element] under conditions that ensure that each compound combination [entity/] test cell [element] contacting is segregated from the others,
- (e) detecting or measuring a property of the test cells [element], and
- (f) selecting [identifying] combinations of compounds [entities] that cause an effect on said property of the test cells [element] that is different from the effect of each compound [an entity] of the combination by itself.

2. (Amended) The method of claim 1, wherein steps (b) and (d) comprise sequentially contacting said compounds [entities] with said test cells [element], thereby creating said array in the presence of said test cells [element].

5. (Amended) The method of claim 1 [4], wherein said detecting step (e) is performed by a cyto blot assay.

6. (Amended) The method of claim 1 [4], wherein said detecting step (e) is performed by a reporter gene assay.

7. (Amended) The method of claim 1 [4], wherein said detecting step (e) is performed by a fluorescence resonance energy transfer assay.

8. (Amended) The method of claim 1 [4], wherein said detecting step (e) is performed by detecting a fluorescent calcium-binding indicator dye.

9. (Amended) The method of claim 1 [4], wherein said detecting step (e) employs fluorescence microscopy.

10. (Amended) The method of claim 1 [4], wherein step (e) employs expression profiling.

11. (Amended) The method of claim 1 [4], wherein said cells [cell is a] are human cells [cell].

12. (Amended) The method of claim 1 [4], wherein said cells are [cell is] selected from the group consisting of [a] cancer cells [cell], [an] immune cells [cell], neurons [a neuron], and fibroblasts [a fibroblast].

18. (Amended) The method of claim 1 [17], wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

20. (Amended) The method of claim 1, wherein at least one of said compounds is [entities is a compound] employed in purified form.

22. (Amended) The method of claim 1, wherein said [entities are] compounds are provided as components of mixtures.

28. (Amended) A method for screening two-compound [two-entity] or higher order combinations for biological activity, said method comprising the steps of:

(a) creating an array of at least 200 unique two-compound [two-entity] or higher order combinations from a set of compounds [entities],

(b) providing [a] living test cells [element comprising one or more distinct biological moieties],

(c) contacting said array of combinations of compounds [entities] with said test cells [element] under conditions that ensure that each compound combination [entity]/test cell [element] contacting is segregated from the others,

(d) detecting or measuring a property of the test cells [element], and

(e) selecting [identifying] combinations of compounds [entities] that cause an effect on said property of the test cells [element] that is different from the effect of each compound [an entity] of the combination by itself.

29. (Amended) The method of claim 28, wherein steps (a) – (c) comprise sequentially contacting said compounds [entities] with said test cells [element], thereby creating said array in the presence of said test cells [element].

30. (Amended) The method of claim 28, further comprising the step of (f) repeating step (a) through (e) at least twice, wherein, in step (a), said array of at least 200 combinations is different in each repetition.

35. (Amended) The method of claim 28 [34], wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

37. (Amended) The method of claim 28, wherein at least one of said compounds [entities] is [a compound] employed in purified form.

39. (Amended) The method of claim 28, wherein said [entities are] compounds are provided as components of mixtures.

40. (Amended) The method of claim 39 [38], wherein said mixtures are natural product extracts.

48. (Amended) A method for screening two-compound [two-entity] or higher order combinations for biological activity, said method comprising the steps of:

- (a) creating an array of at least 49 unique two-compound [two-entity] or higher order combinations,
- (b) providing [a] living test cells [element comprising one or more distinct biological moieties],
- (c) contacting said array of combinations of compounds [entities] with said test cells [element] under conditions that ensure that each compound combination [entity]/test cell [element] contacting is segregated from the others,
- (d) detecting or measuring a property of the test cells [element],
- (e) selecting [identifying] combinations of compounds [entities] that cause an effect on said property of the test cells [element] that is different from the effect of each compound [an entity] of the combination by itself, and
- (f) repeating steps (a) through (e) at least 25 times over a [one week] one-week period, using a different array in each repetition.

51. (Amended) The method of claim 48 [50], wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

53. (Amended) The method of claim 48, wherein said [entities are] compounds are employed in purified form.

54. (Amended) The method of claim 48, wherein said [entities are] compounds are provided as components of mixtures.

55. (Amended) The method of claim 54, wherein said mixtures are natural product extracts.

60. (Amended) A method for screening two-compound [two-entity] or higher order combinations for biological activity, said method comprising the steps of:

- (a) creating an array of at least 10,000 unique two-compound [two-entity] or higher order combinations from a set of compounds [entities],
- (b) providing [a] living test cells [element comprising one or more distinct biological moieties],

- (c) contacting said array of combinations of compounds [entities] with said test cells [element] under conditions that ensure that each compound combination [entity]/test cell [element] contacting is segregated from the others,
- (d) detecting or measuring a property of the test cells [element],
- (e) selecting [identifying] combinations of compounds [entities] that cause an effect on said property of the test cells [element] that is different from the effect of each compound [an entity] of the combination by itself, and
- (f) repeating steps (a) through (e) at least twice over a period of ten days or less, wherein, in step (a), said array of at least 10,000 two-compound or higher order [two-entity] combinations is different in two or more repetitions.

61. (Amended) A method for screening combinations of compounds [entities] for biological activity, said method comprising the steps of:

- (a) providing [a] living test cells [element comprising one or more distinct biological moieties],
- (b) contacting said test cells [element] with at least 100 compounds [entities] under conditions that ensure that each compound [entity]/test cell [element] contacting is segregated from the others,
- (c) detecting or measuring a property of said test cells [element],
- (d) selecting compounds [entities] that cause a change in said property relative to said property of said test cells [element] not contacted with said compounds [entities],
- (e) creating an array of at least 49 unique two-compound [two-entity] or higher order combinations from the identified compounds [entities],
- (f) contacting said array of combinations of compounds [entities] with [a] test cells [element] under conditions that ensure that each compound [entity] combination/test cell [element] contacting is segregated from the others,
- (g) detecting or measuring a property of the test cells [element] of step (f), and
- (h) selecting [identifying] combinations of compounds [entities] that cause an effect on said property of step (g) that is different from the effect of each compound [an entity] of the combination by itself.

62. (Amended) The method of claim 61, wherein the test cells [element] of step (a) are [is] the same as the test cells [element] of step (f).

Clean version of all pending claims

1. A method of screening two-compound or higher order combinations for biological activity using at least seven compounds in at least a seven-by-seven combinational array comprising at least forty-nine unique combinations of compounds, said method comprising the steps of:

- (a) providing said compounds,
- (b) creating said array of combinations of compounds,
- (c) providing living test,
- (d) contacting said array of combinations of compounds with said test cells under conditions that ensure that each compound combination/test cell contacting is segregated from the others,
- (e) detecting or measuring a property of the test cells, and
- (f) selecting combinations of compounds that cause an effect on said property of the test cells that is different from the effect of each compound of the combination by itself.

2. The method of claim 1, wherein steps (b) and (d) comprise sequentially contacting said compounds with said test cells, thereby creating said array in the presence of said test cells.

5. The method of claim 1, wherein said detecting step (e) is performed by a cytoblot assay.

6. The method of claim 1, wherein said detecting step (e) is performed by a reporter gene assay.

7. The method of claim 1, wherein said detecting step (e) is performed by a fluorescence resonance energy transfer assay.

8. The method of claim 1, wherein said detecting step (e) is performed by detecting a fluorescent calcium-binding indicator dye.

9. The method of claim 1, wherein said detecting step (e) employs fluorescence microscopy.

10. The method of claim 1, wherein step (e) employs expression profiling.

11. The method of claim 1, wherein said cells are human cells.

12. The method of claim 1, wherein said cells are selected from the group consisting of cancer cells, immune cells, neurons, and fibroblasts.

14. The method of claim 1, wherein one or both of steps (b) and (d) is carried out using a robotics system.

15. The method of claim 1, wherein one or both of steps (b) and (d) is carried out using microfluidics.

16. The method of claim 1, wherein one or both of steps (b) and (d) is carried out using ink-jet printer technology.

18. The method of claim 1, wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

20. The method of claim 1, wherein at least one of said compounds is employed in purified form.

21. The method of claim 20, wherein each of said compounds is employed in purified form.

22. The method of claim 1, wherein said compounds are provided as components of mixtures.

23. The method of claim 22, wherein said mixtures are natural product extracts.

24. The method of claim 1, wherein said effect is a synergistic effect.

28. A method for screening two-compound or higher order combinations for biological activity, said method comprising the steps of:

- (a) creating an array of at least 200 unique two-compound or higher order combinations from a set of compounds,
- (b) providing living test cells,
- (c) contacting said array of combinations of compounds with said test cells under conditions that ensure that each compound combination/test cell contacting is segregated from the others,
- (d) detecting or measuring a property of the test cells, and
- (e) selecting combinations of compounds that cause an effect on said property of the test cells that is different from the effect of each compound of the combination by itself.

29. The method of claim 28, wherein steps (a) – (c) comprise sequentially contacting said compounds with said test cells, thereby creating said array in the presence of said test cells.

30. The method of claim 28, further comprising the step of (f) repeating step (a) through (e) at least twice, wherein, in step (a), said array of at least 200 combinations is different in each repetition.

31. The method of claim 30, wherein at least two repetitions of step (f) occur within 10 days of each other.

32. The method of claim 28, wherein said array comprises at least 400 unique combinations.

33. The method of claim 28, wherein said array comprises at least 1540 unique combinations.

35. The method of claim 28, wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

37. The method of claim 28, wherein at least one of said compounds is employed in purified form.

38. The method of claim 28, wherein each of said compounds is employed in purified form.

39. The method of claim 28, wherein said compounds are provided as components of mixtures.

40. The method of claim 39, wherein said mixtures are natural product extracts.

41. The method of claim 28, wherein said effect is a synergistic effect.

42. The method of claim 28, wherein one or both of steps (a) and (c) is carried out using a robotics system.

43. The method of claim 28, wherein one or both of steps (a) and (c) is carried out using microfluidics.

44. The method of claim 28, wherein one or both of steps (a) and (c) is carried out using ink-jet printer technology.

48. A method for screening two-compound or higher order combinations for biological activity, said method comprising the steps of:

(a) creating an array of at least 49 unique two-compound or higher order combinations,

- (b) providing living test cells,
- (c) contacting said array of combinations of compounds with said test cells under conditions that ensure that each compound combination/test cell contacting is segregated from the others,
- (d) detecting or measuring a property of the test cells,
- (e) selecting combinations of compounds that cause an effect on said property of the test cells that is different from the effect of each compound of the combination by itself, and
- (f) repeating steps (a) through (e) at least 25 times over a one-week period, using a different array in each repetition.

49. The method of claim 48, wherein steps (a) through (e) are repeated at least 100 times over a 30-day period, using a different array in each repetition.

51. The method of claim 48, wherein said compounds are selected from the group consisting of non-polymeric organic compounds, lipids, carbohydrates, peptides, inorganic compounds, and oligonucleotides.

53. The method of claim 48, wherein said compounds are employed in purified form.

54. The method of claim 48, wherein said compounds are provided as components of mixtures.

55. The method of claim 54, wherein said mixtures are natural product extracts.

56. The method of claim 48, wherein said effect is a synergistic effect.

57. The method of claim 48, wherein one or both of steps (a) and (c) is carried out using a robotics system.

58. The method of claim 48, wherein one or both of steps (a) and (c) is carried out using microfluidics.

59. The method of claim 48, wherein one or both of steps (a) and (c) is carried out using ink-jet printer technology.

60. A method for screening two-compound or higher order combinations for biological activity, said method comprising the steps of:

- (a) creating an array of at least 10,000 unique two-compound or higher order combinations from a set of compounds,
- (b) providing living test cells,

(c) contacting said array of combinations of compounds with said test cells under conditions that ensure that each compound combination/test cell contacting is segregated from the others,

(d) detecting or measuring a property of the test cells,

(e) selecting combinations of compounds that cause an effect on said property of the test cells that is different from the effect of each compound of the combination by itself, and

(f) repeating steps (a) through (e) at least twice over a period of ten days or less, wherein, in step (a), said array of at least 10,000 two-compound or higher order combinations is different in two or more repetitions.

61. A method for screening combinations of compounds for biological activity, said method comprising the steps of:

(a) providing living test cells,

(b) contacting said test cells with at least 100 compounds under conditions that ensure that each compound/test cell contacting is segregated from the others,

(c) detecting or measuring a property of said test cells,

(d) selecting compounds that cause a change in said property relative to said property of said test cells not contacted with said compounds,

(e) creating an array of at least 49 unique two-compound or higher order combinations from the identified compounds,

(f) contacting said array of combinations of compounds with test cells under conditions that ensure that each compound combination/test cell contacting is segregated from the others,

(g) detecting or measuring a property of the test cells of step (f), and

(h) selecting combinations of compounds that cause an effect on said property of step (g) that is different from the effect of each compound of the combination by itself.

62. The method of claim 61, wherein the test cells of step (a) are the same as the test cells of step (f).

63. The method of claim 61, wherein the property of step (c) is the same as the property of step (g).

64. The method of claim 1, wherein at least one of said compounds is a small molecule.

65. The method of claim 64, wherein said small molecule is an FDA-approved drug.

66. The method of claim 64, wherein each of said compounds is a small molecule.

67. The method of claim 66, wherein said small molecules are FDA-approved drugs.

68. The method of claim 28, wherein at least one of said compounds is a small molecule.

69. The method of claim 68, wherein said small molecule is an FDA-approved drug.

70. The method of claim 68, wherein each of said compounds is a small molecule.

71. The method of claim 70, wherein said small molecules are FDA-approved drugs.

72. The method of claim 48, wherein at least one of said compounds is a small molecule.

73. The method of claim 72, wherein said small molecule is an FDA-approved drug.

74. The method of claim 72, wherein each of said compounds is a small molecule.

75. The method of claim 74, wherein said small molecules are FDA-approved drugs.

76. The method of claim 48, wherein at least one of said compounds is a small molecule.

77. The method of claim 76, wherein said small molecule is an FDA-approved drug.

78. The method of claim 76, wherein each of said compounds is a small molecule.

79. The method of claim 78, wherein said small molecules are FDA-approved drugs.

80. The method of claim 60, wherein at least one of said compounds is a small molecule.

81. The method of claim 80, wherein said small molecule is an FDA-approved drug.

82. The method of claim 80, wherein each of said compounds is a small molecule.

83. The method of claim 82, wherein said small molecules are FDA-approved drugs.

84. The method of claim 1, wherein said creating step (b) comprises contacting at least seven of said compounds with each other in a pair-wise manner.

85. The method of claim 1, wherein each of said combinations screened for biological activity is a two-compound combination.

86. The method of claim 28, wherein each of said combinations screened for biological activity is a two-compound combination.

87. The method of claim 1, wherein each of said combinations screened for biological activity is a three-compound combination.

88. The method of claim 28, wherein each of said combinations screened for biological activity is a three-compound combination.